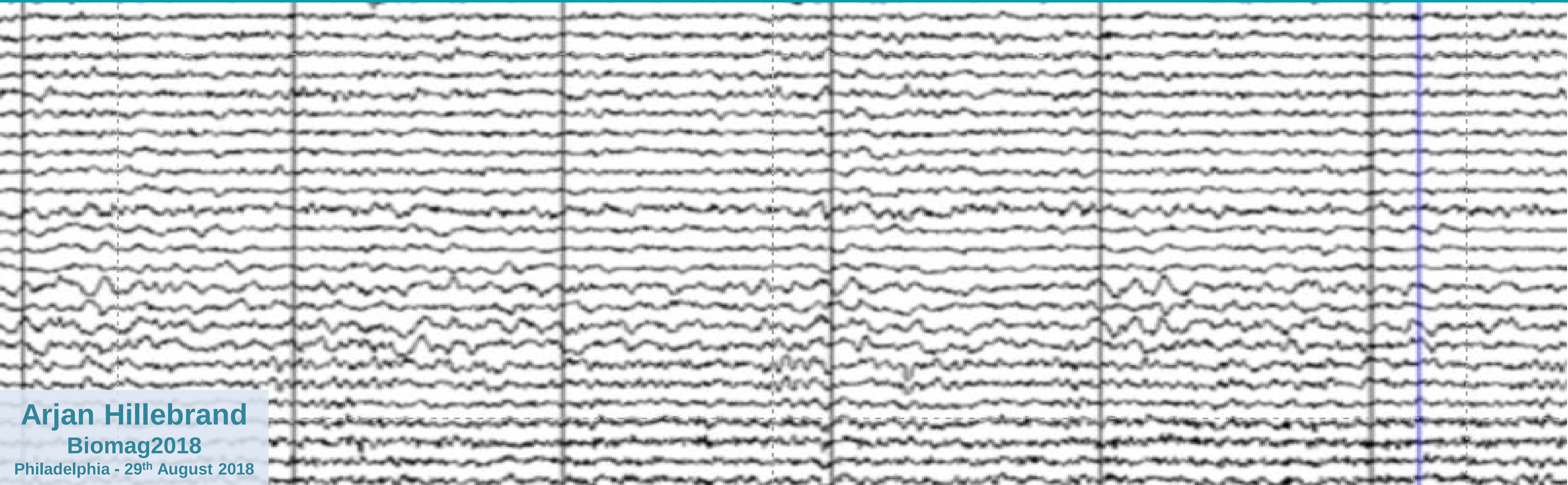
Amsterdam UMC
University Medical Centers

Clinical use of MEG
in the memory and MS outpatient clinics



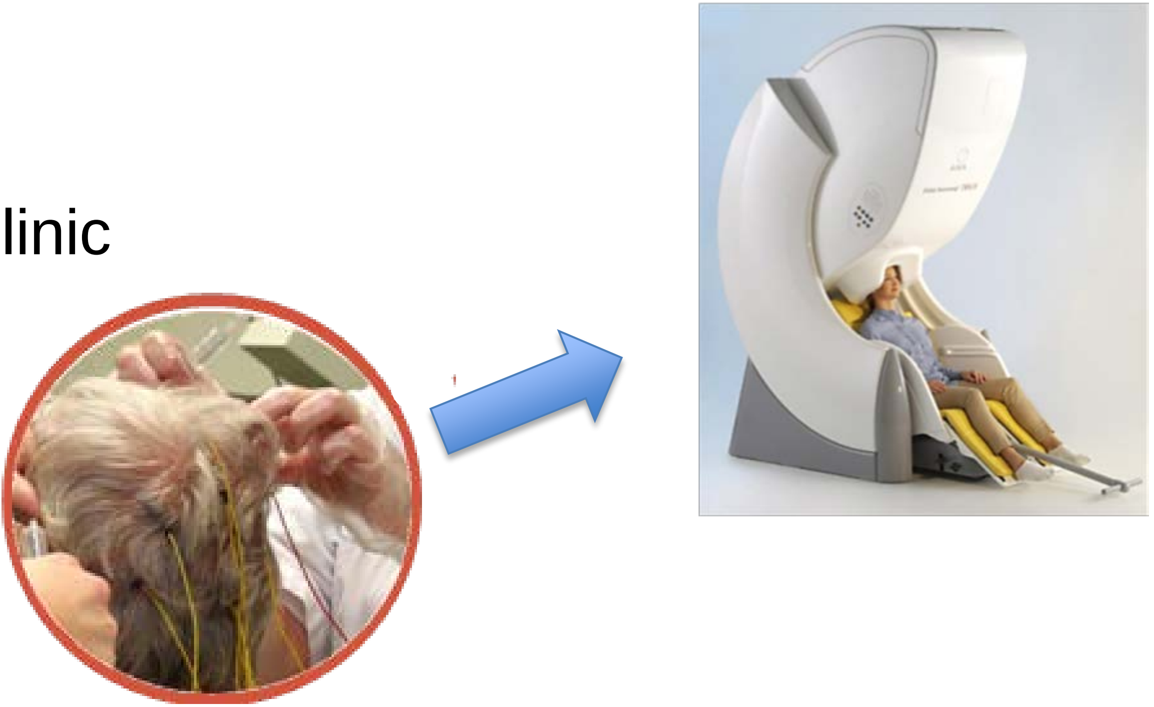
Arjan Hillebrand

Biomag2018

Philadelphia - 29th August 2018

Background

- Established clinical application of MEG: diagnosis & pre-surgical evaluation for epilepsy surgery
- MEG often considered to be too complicated/expensive for other clinical applications
- Solution: use established clinical EEG protocols with MEG
- Two examples:
    - Memory clinic
    - MS outpatient clinic

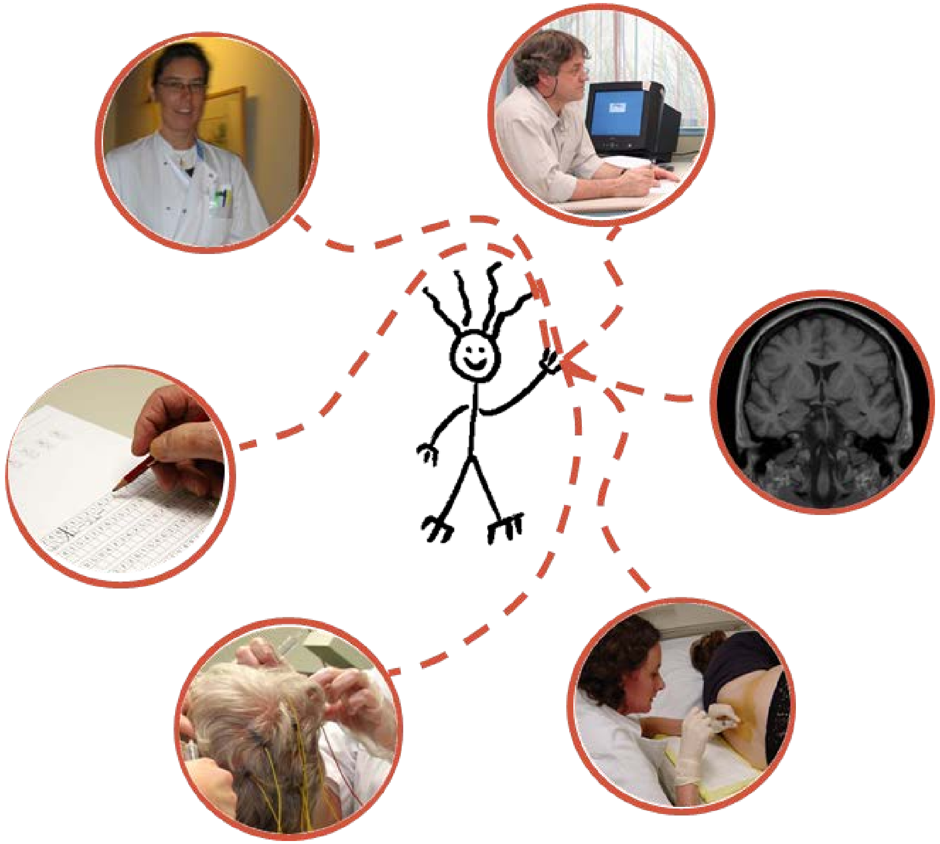


Disclosures

- Alzheimercentrum has received research support from Boehringer Ingelheim and Probiodrug AG
- Funding from ZonMW (Memorabel)

- MS centrum has received research support from the Dutch MS Research Foundation

EEG in the memory clinic



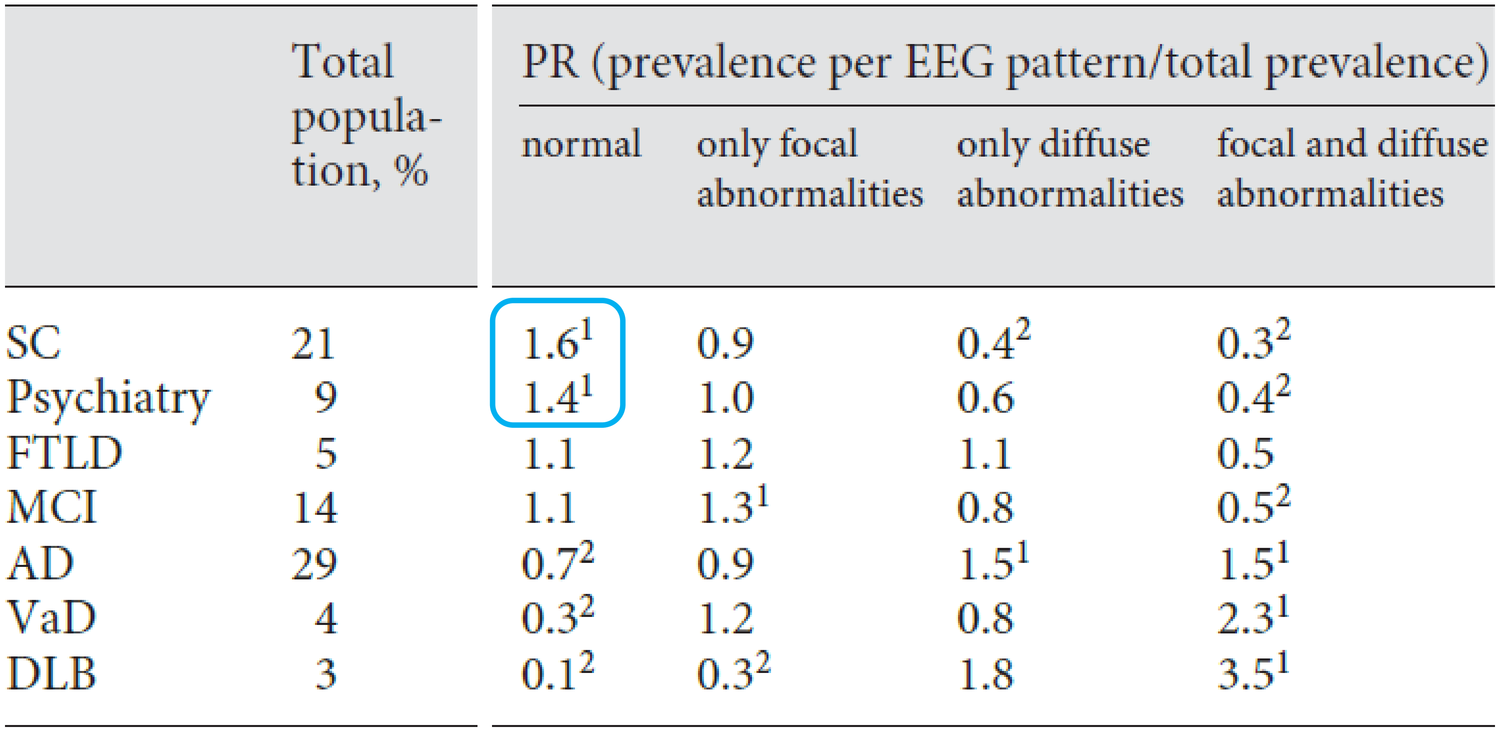
Multidisciplinary meeting:
Diagnosis

EEG

- Since 2001
- 21-channels
- Short registration:15 minutes
- Eyes closed, in ‘rest’
- Reactivity to eyes opening
- Memory test
- Downside: drowsiness!

Van der Flier *et al.*, 2014

Visual analysis of EEG for diagnosis



	Total population, %	PR (prevalence per EEG pattern/total prevalence)			
		normal	only focal abnormalities	only diffuse abnormalities	focal and diffuse abnormalities
SC	21	1.6^1	0.9	0.4^2	0.3^2
Psychiatry	9	1.4^1	1.0	0.6	0.4^2
FTLD	5	1.1	1.2	1.1	0.5
MCI	14	1.1	1.3^1	0.8	0.5^2
AD	29	0.7^2	0.9	1.5^1	1.5^1
VaD	4	0.3^2	1.2	0.8	2.3^1
DLB	3	0.1^2	0.3^2	1.8	3.5^1

Liedorp *et al.*, 2009

Visual analysis of EEG for diagnosis

	Total population, %	PR (prevalence per EEG pattern/total prevalence)			
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SC	21	1.6[1]			
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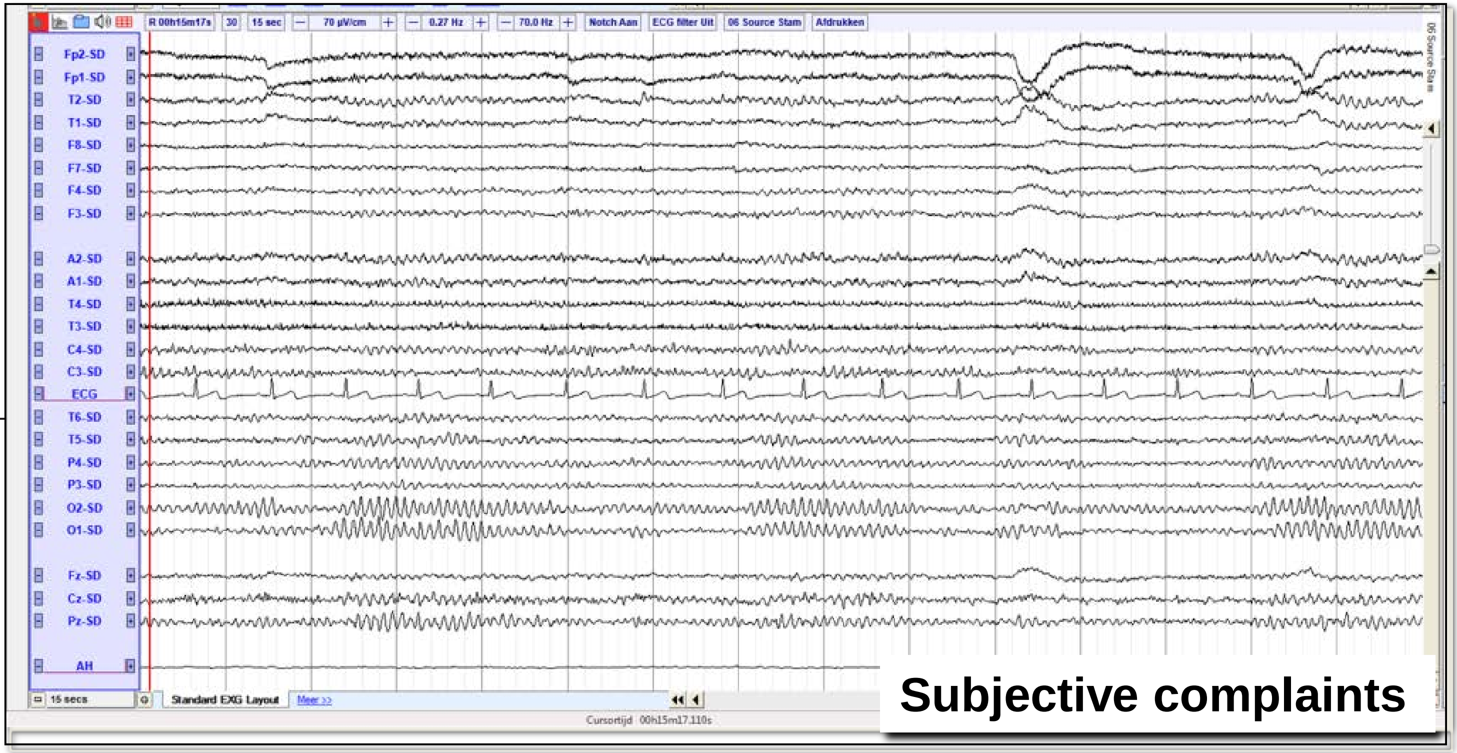
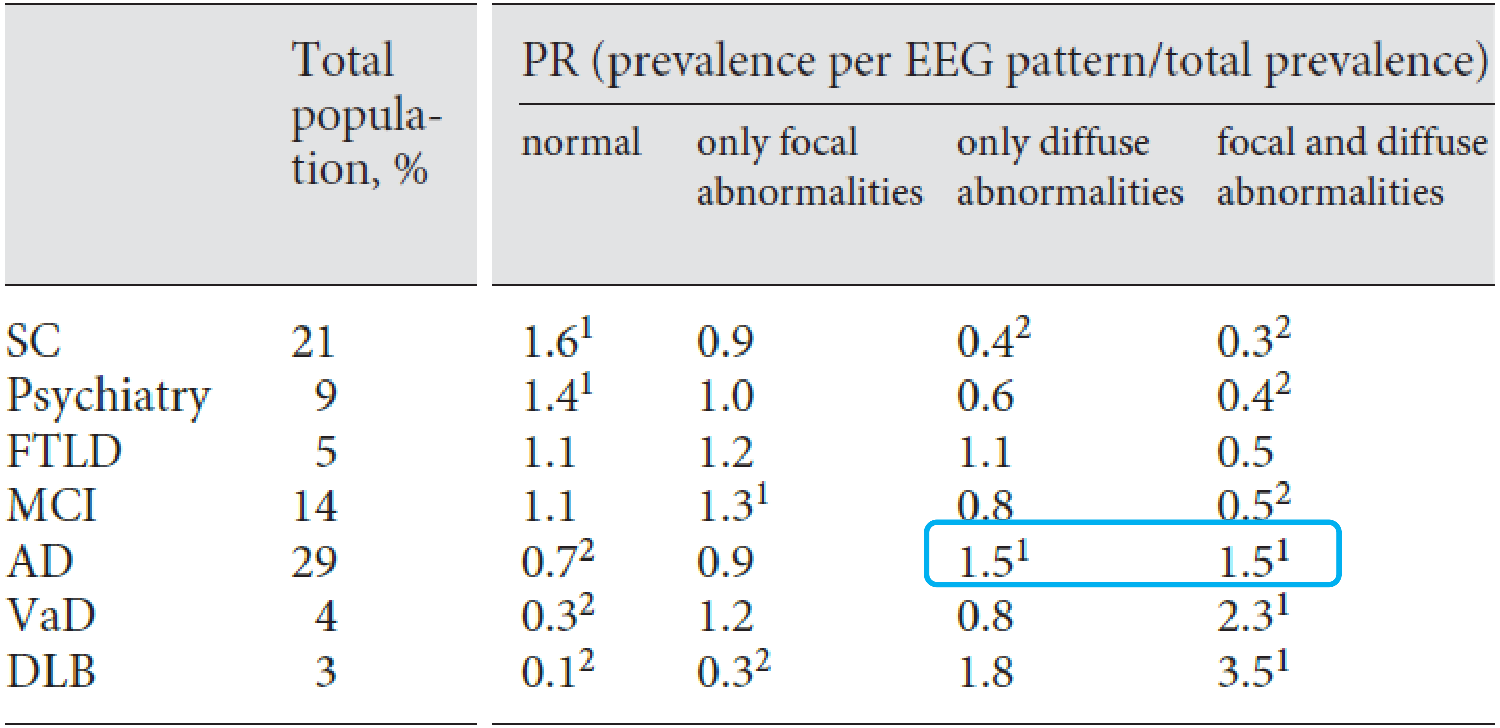
FTLD	5	1.1			
MCI	14	1.1			
AD	29	0.7[2]			
VaD	4	0.3[2]			
DLB	3	0.1[2]			



Subjective complaints

Liedorp *et al.*, 2009

Visual analysis of EEG for diagnosis



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Visual analysis of EEG for diagnosis

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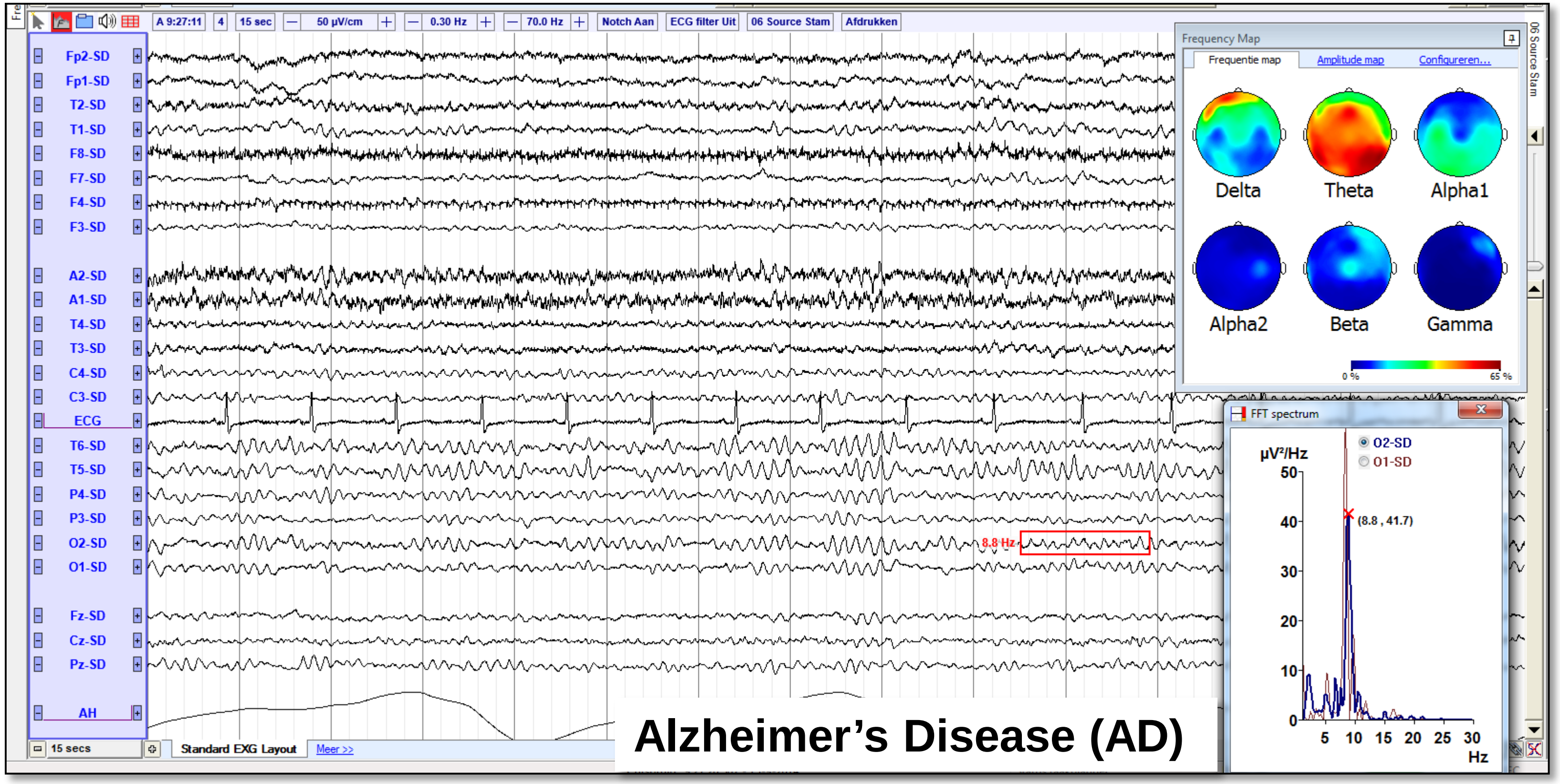
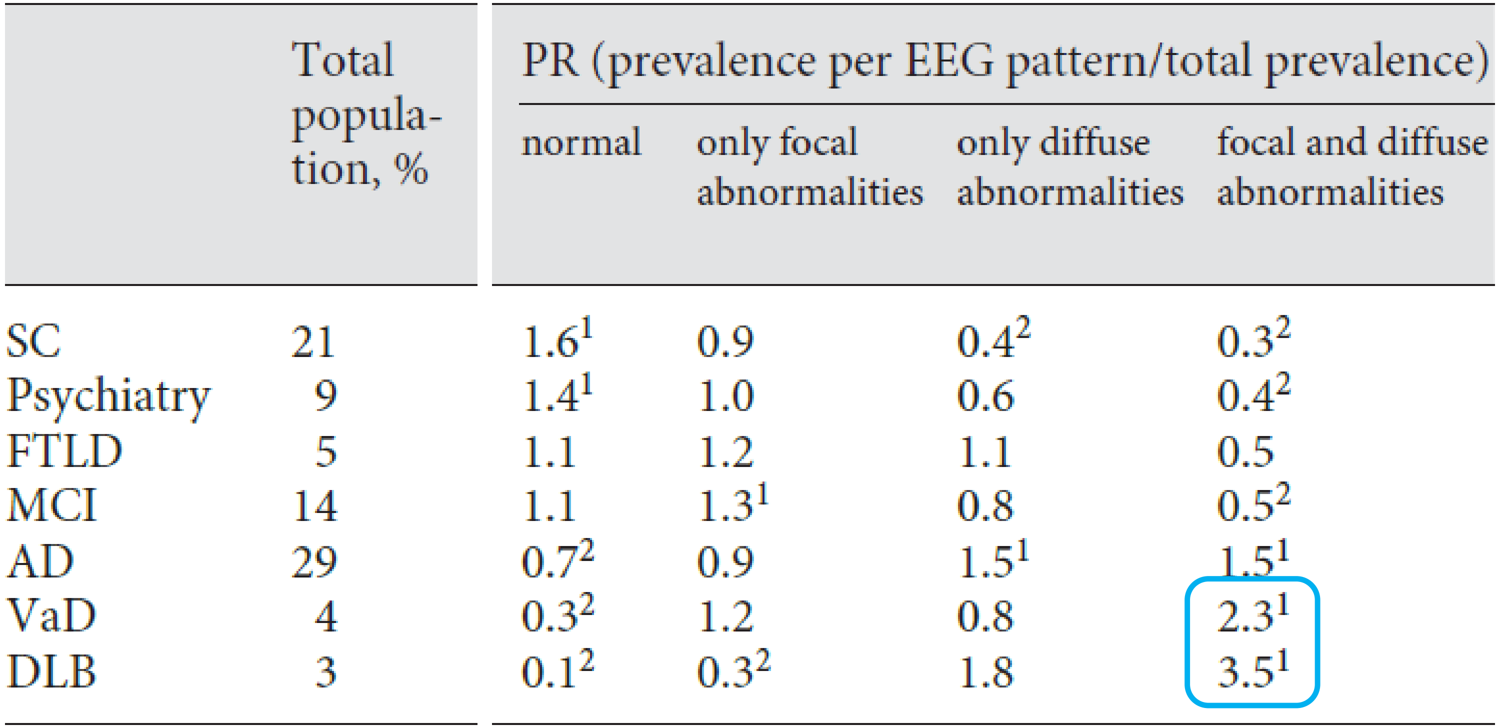


Alzheimer's Disease (AD)

Visual analysis of EEG for diagnosis



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Visual analysis of EEG for diagnosis

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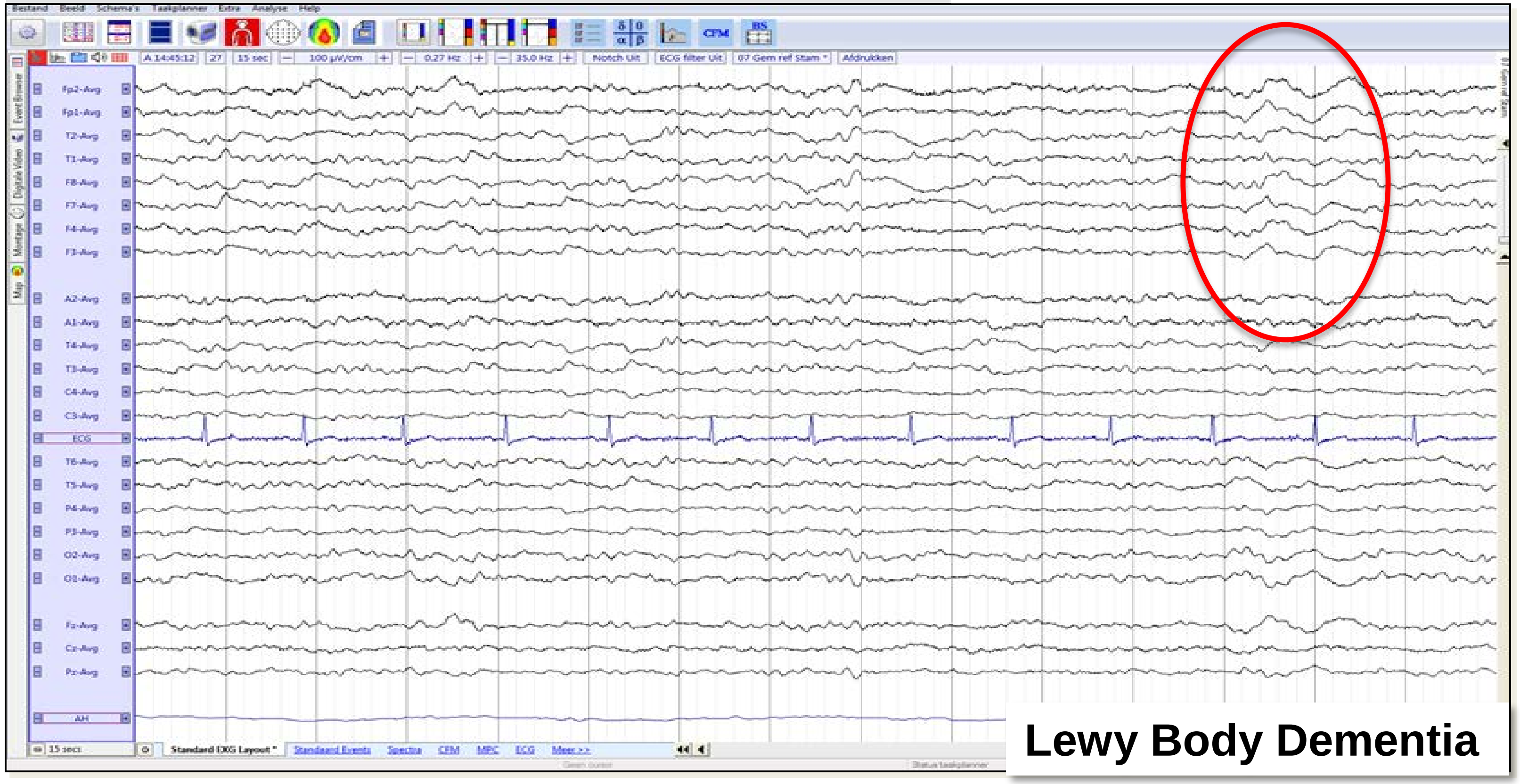
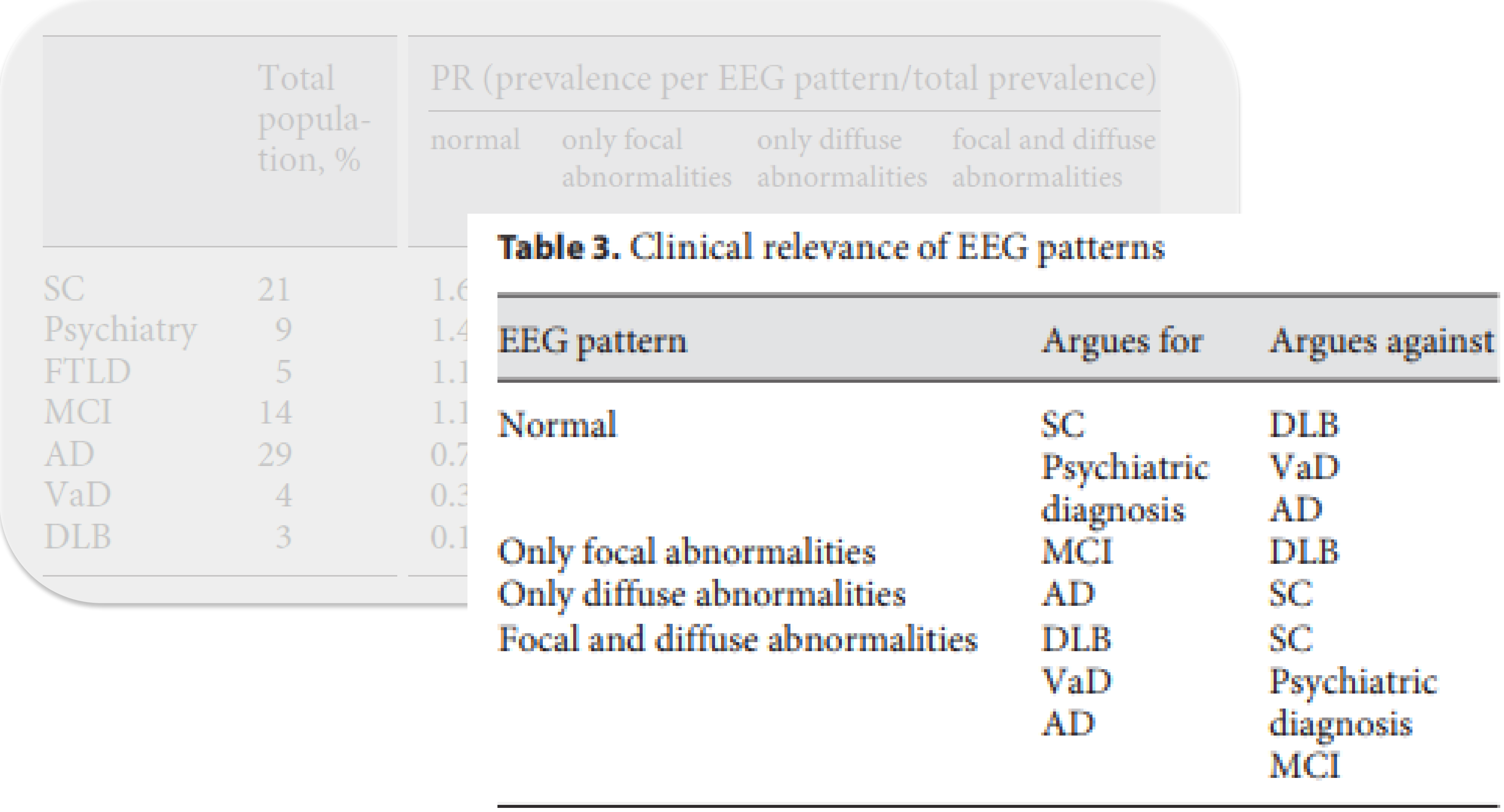


Lewy Body Dementia

Visual analysis of EEG for diagnosis



	Total population, %	PR (prevalence per EEG pattern/total prevalence)			
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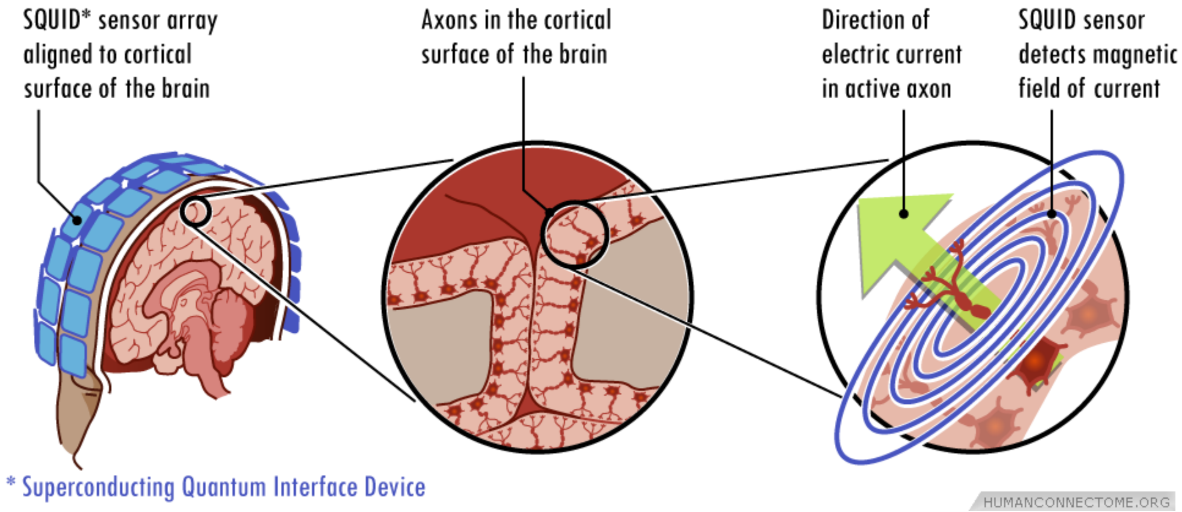
SC	21	1.6			
Psychiatry	9	1.4			
FTLD	5	1.1			
MCI	14	1.1			
AD	29	0.7			
VaD	4	0.3			
DLB	3	0.1			

Table 3. Clinical relevance of EEG patterns

EEG pattern	Argues for	Argues against
Normal	SC Psychiatric diagnosis	DLB VaD AD
Only focal abnormalities	MCI	DLB
Only diffuse abnormalities	AD	SC
Focal and diffuse abnormalities	DLB VaD AD	SC Psychiatric diagnosis MCI

Magnetoencephalography (MEG)


SQUID* sensor array aligned to cortical surface of the brain
Axons in the cortical surface of the brain
Direction of electric current in active axon
SQUID sensor detects magnetic field of current
* Superconducting Quantum Interface Device
HUMANCONNECTOME.ORG

Advantages over 21-channel EEG:

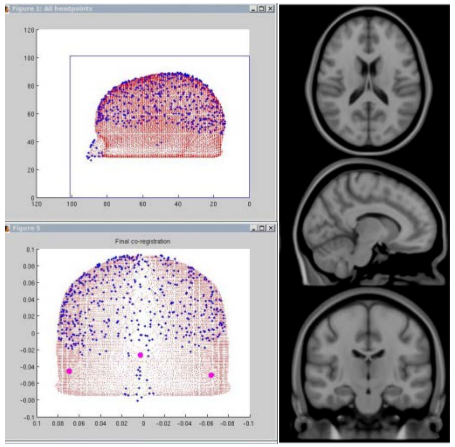
- Higher spatial resolution (100+ sensors)
- Reference-free
- Sensitive to activity in deeper structures
- Signals less distorted by skull and muscle activity
- Patient friendly

Engels *et al.,* 2016; Hillebrand et al., 2016

Magnetoencephalography (MEG)

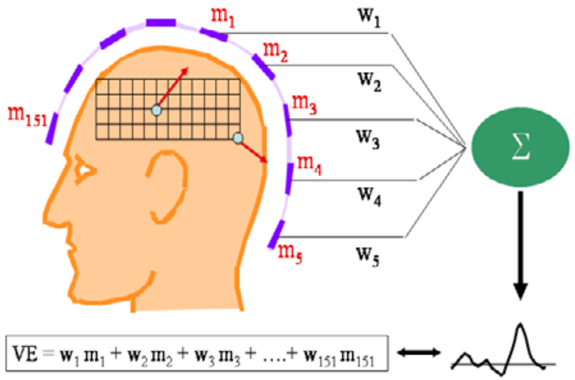
Raw MEG data, tSSS filter

Co-registration with MRI



Brain atlas: ‘virtual electrodes’

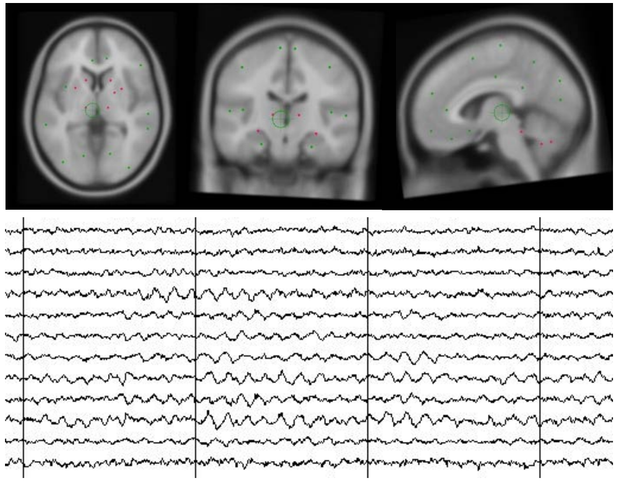
Source reconstruction: Beamforming



$VE = w_1 m_1 + w_2 m_2 + w_3 m_3 + \ldots + w_{151} m_{151}$

Figure courtesy of Dr. D. Cheyne, University of Toronto (modified)

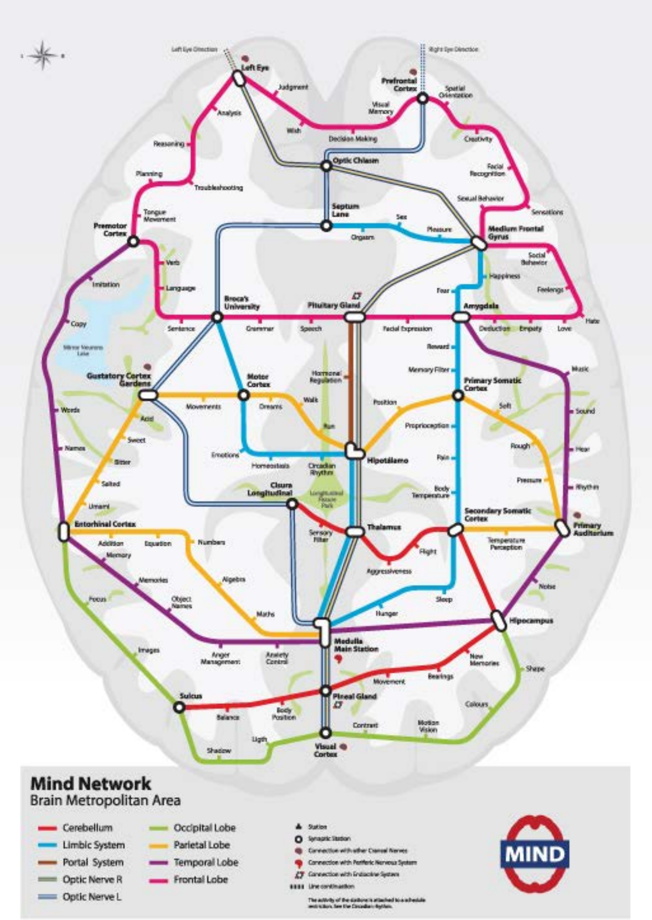
MEG data at source level (90 ROIs)



Hillebrand *et al.*, 2012, 2016; Hillebrand *et al.*, 2005; Douw *et al.*, 2018;

MEG netwerk analysis

Specific hubs are affected in Alzheimer's disease



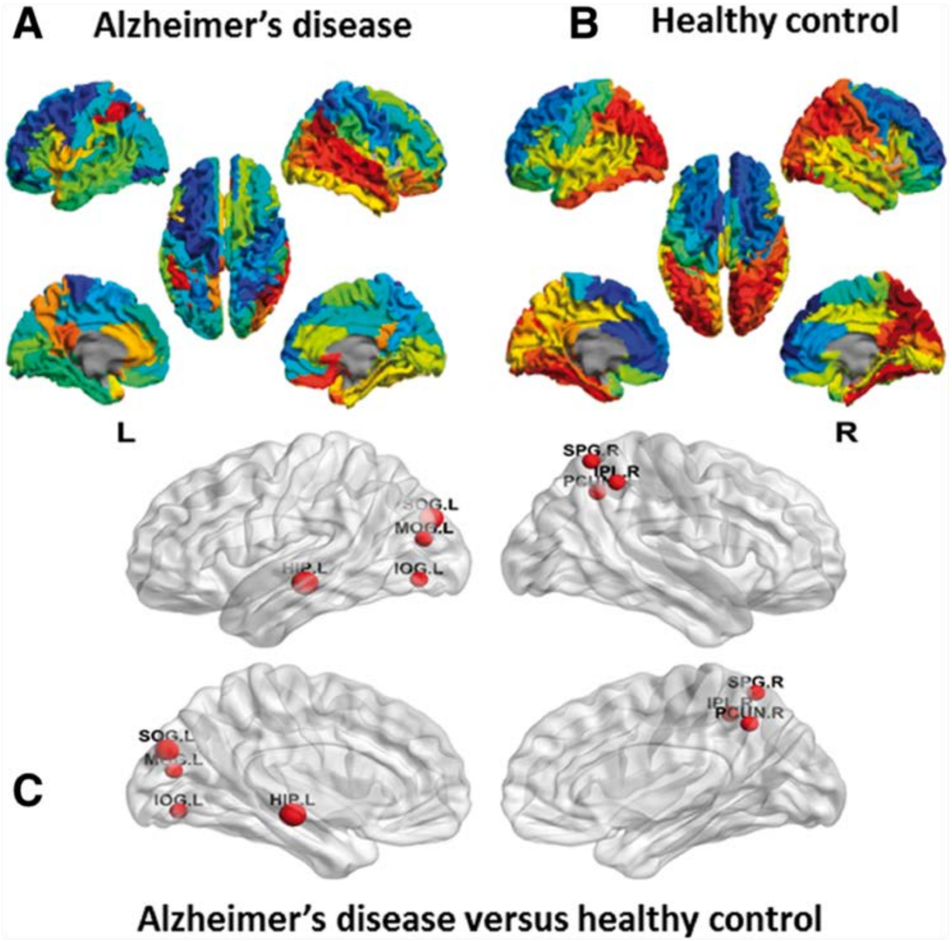


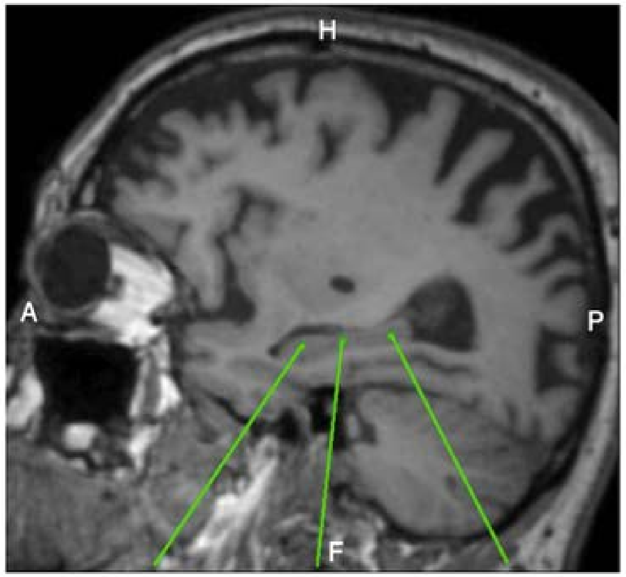
Image: https://miguelandres.com/w/mente-poster/

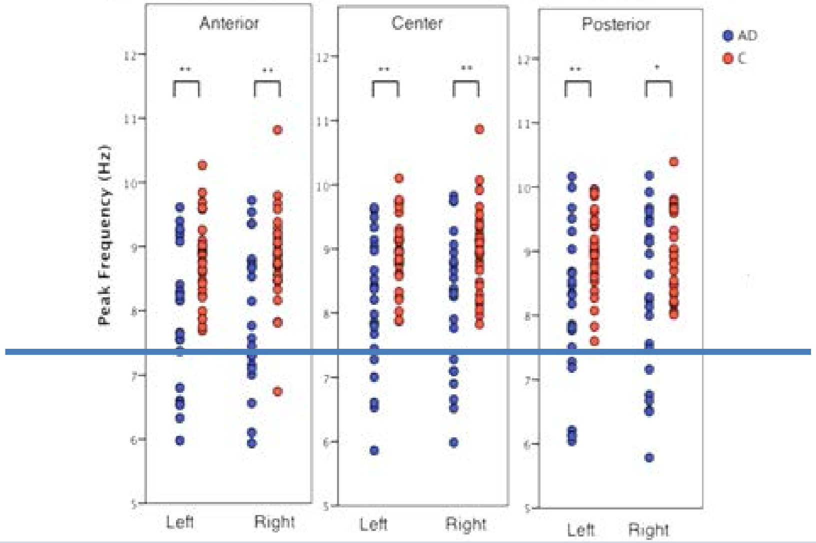
Yu *et al.*, 2017

MEG activity in the hippocampus

in Alzheimer's disease

- 3 'virtual electrodes' in each hippocampus
- Hippocampus:
  - Piek frequency < 7.5 Hz = Alzheimer's disease
  - Correlated better with cognitive decline than cortical activity





Engels *et al.*, 2016

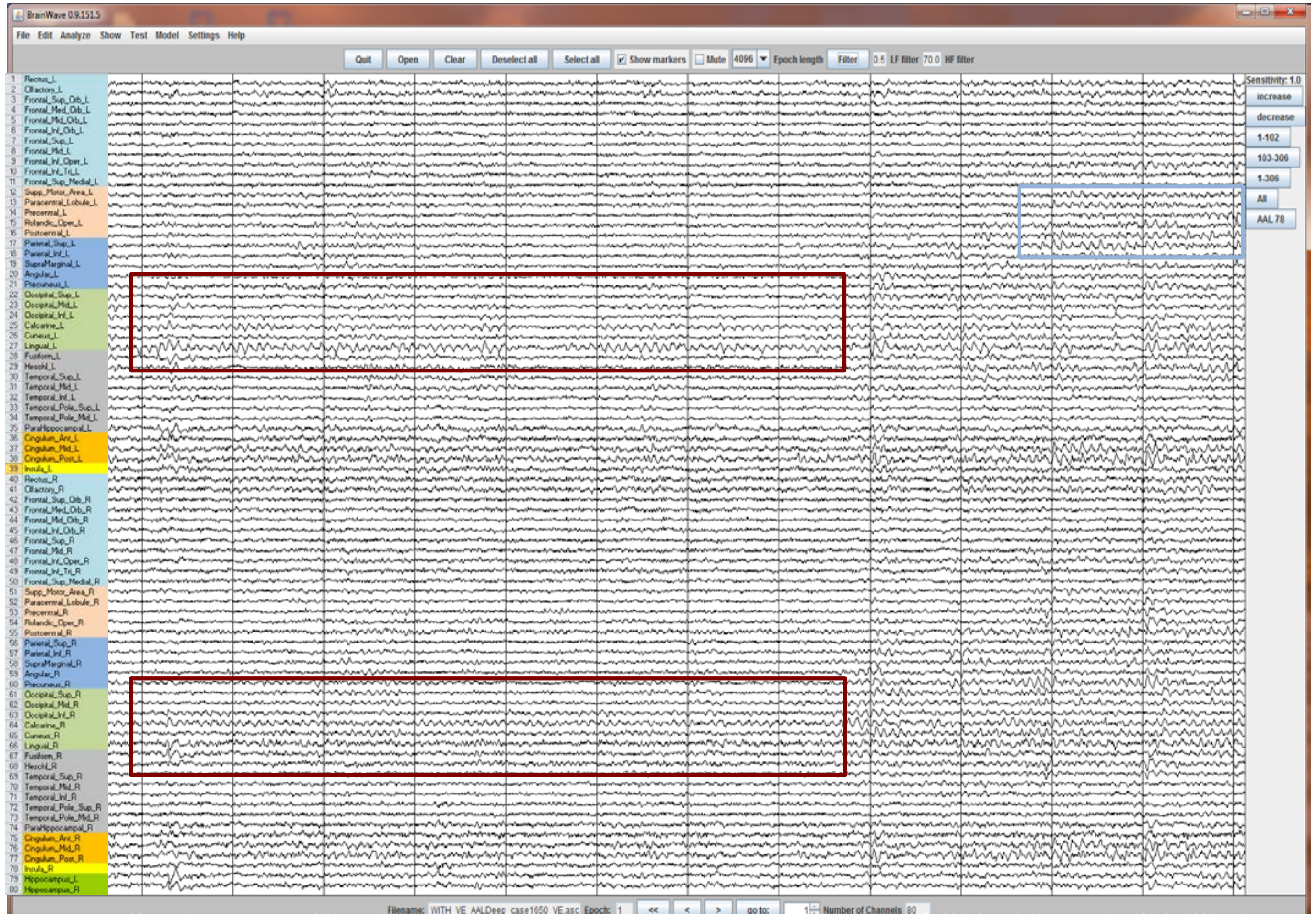
MEG during dayscreening

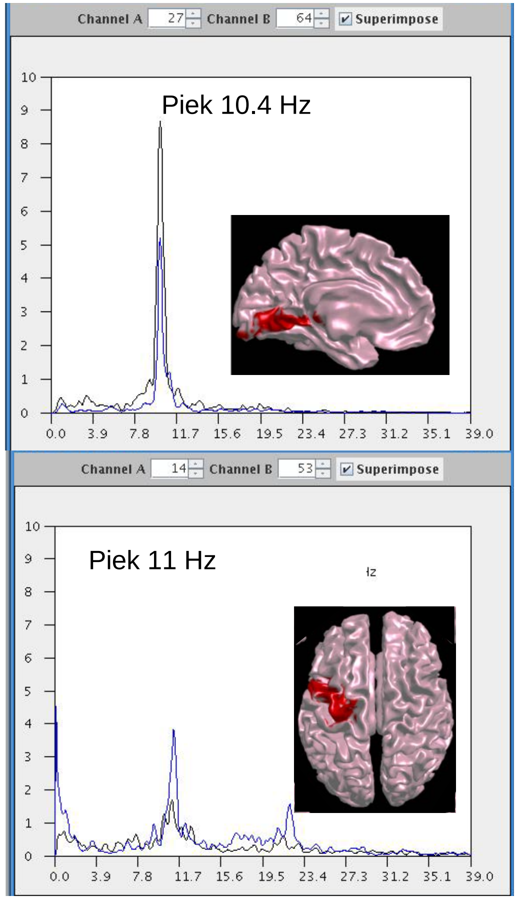
- 2 patients/week, unselected
- Elekta MEG-system: 306 sensors
- 5 min eyes closed, in ‘rest’, 1-2 x eyes open (reactivity)
- 5 min eyes closed
- Memory test

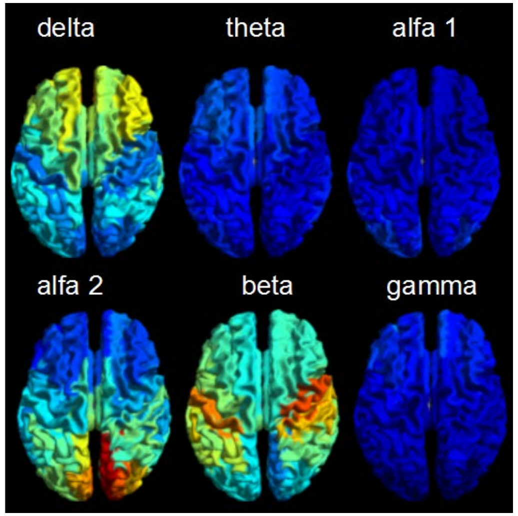
Diagnostic rapport:

- Blind for clinical information
- Except for age, gender and medication use
- Visual and spectral analysis

Casus 1: 53 year old woman





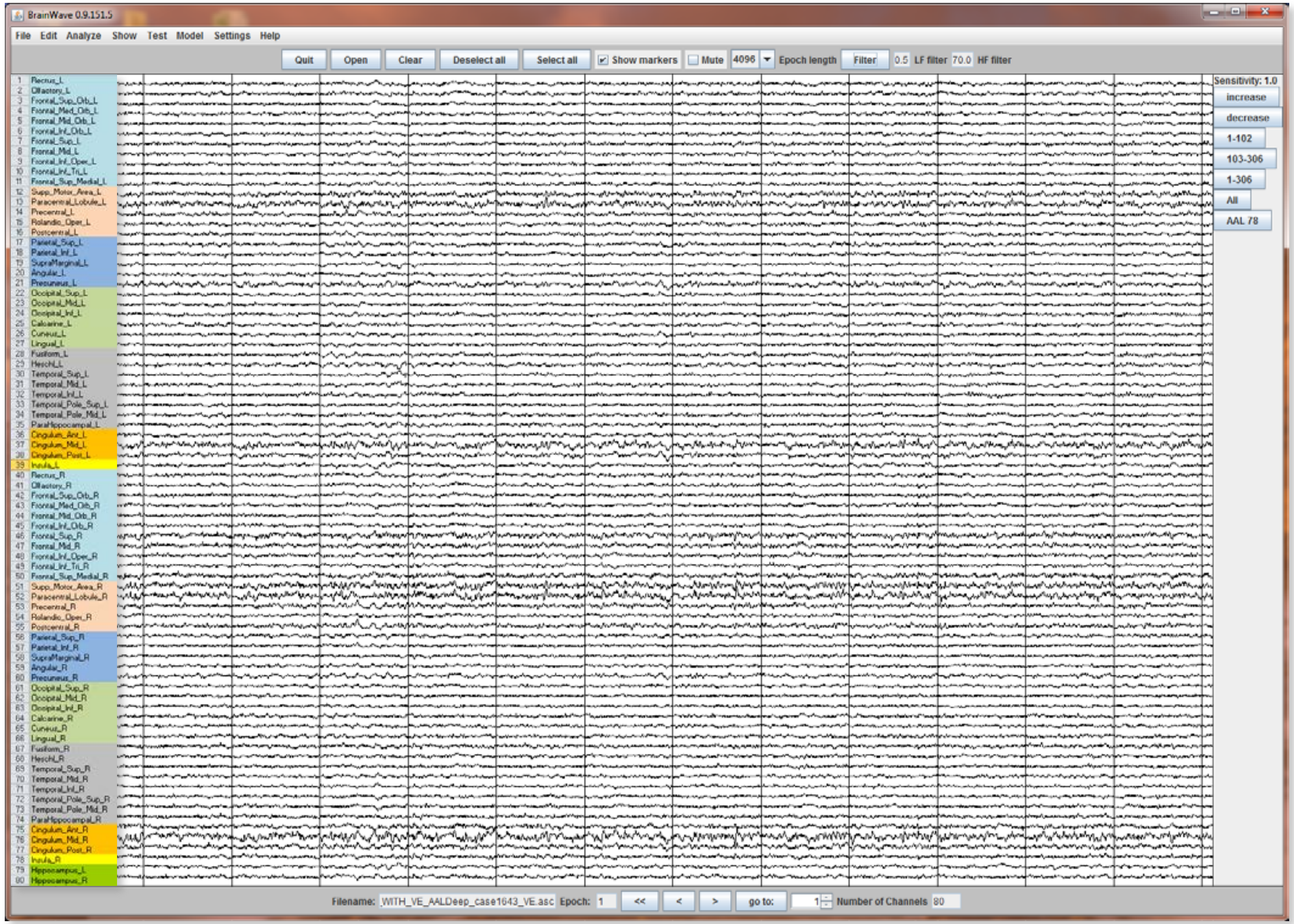


MEG conclusion: normal MEG

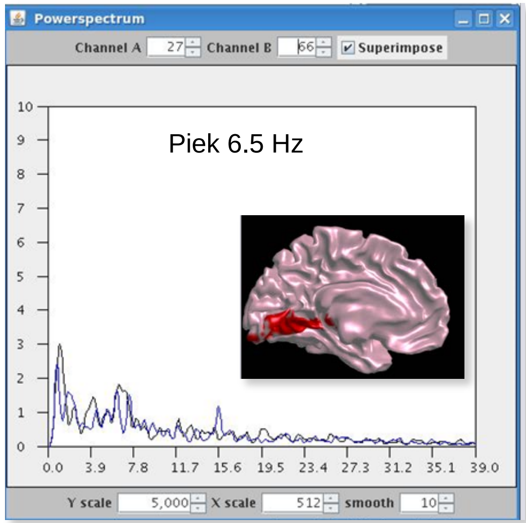
Clinical: memory complaints, no abnormalities in neuropsychological examination or MRI

Diagnosis: subjective memory complaints

Casus 2: 58 year old woman



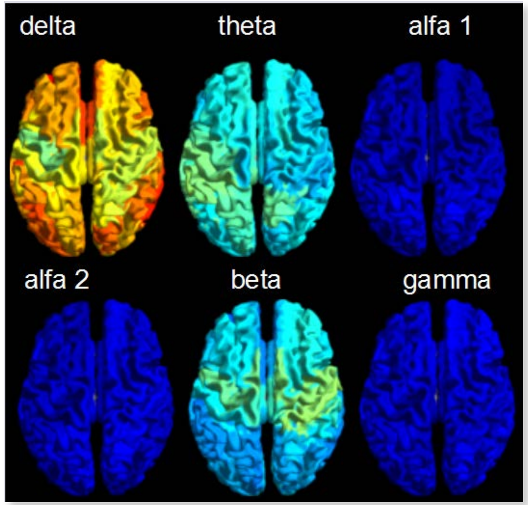
Filename: WITH_VE_AALDeep_case1643_VE.asc Epoch: 1 go to: 1 Number of Channels 80



Channel A 27 Channel B 66

Y scale 5,000 X scale 512 smooth 10

Piek 6.5 Hz



MEG conclusion: diffuse slowing

Clinical: dementia or depression?

Diagnosis: early onset Alzheimer’s disease

Patient cohort

From April 2015: n = 238

	N
Alzheimer’s disease	63
Subjective complaints (SCD)	59
Psychiatric	24
Mild cognitive impairment	27
Frontotemporal dementia	11
Lewy Body dementia	9
Vascular dementia	7
Other diagnosis	36

Conclusions (Part 1)

- Visual analysis of EEG and MEG provides information for differential diagnosis

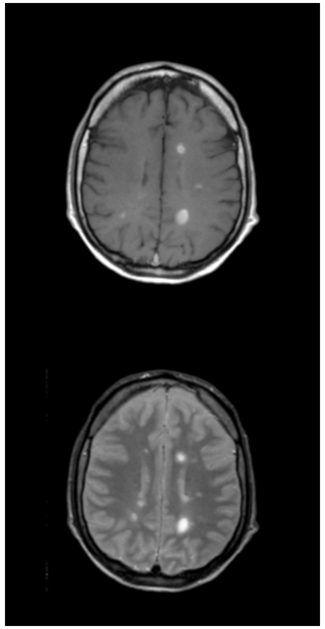
- EEG:
  - Available in any hospital

- MEG:
  - Patient friendly
  - Quick
  - Higher spatial resolution
  - Can focus on disease-specific brain regions (e.g. hippocampus)

- MEG as diagnostic tool for AD versus SCD:
  - Spectral properties in cortical and subcortical areas
  - Reliable and accurate biomarker (*unpublished results*)

Introduction: cognition & MS

- Heterogeneous pathology on in vivo imaging (MRI):



  - **Structural**
    - White and gray matter demyelination
    - Neuronal and axonal degeneration => atrophy
  - **Functional**
    - Functional (network) changes (e.g. Tewarie *et al.*, 2013, 2014, 2015; Hardmeier *et al.*, 2012; Schoonheim *et al.*, 2013)
- Cognitive impairment is frequently present in MS patients (40-70%) (Chiaravalloti & DeLuca, 2008)

Introduction: cognition & MS

Changes in oscillatory activity are present in MS:

- Slowing in MS patients compared to healthy controls, which correlates with cognition.
- Found with both EEG (Colon *et al.*, 1981 and MEG (van der Meer *et al.*, 2013)

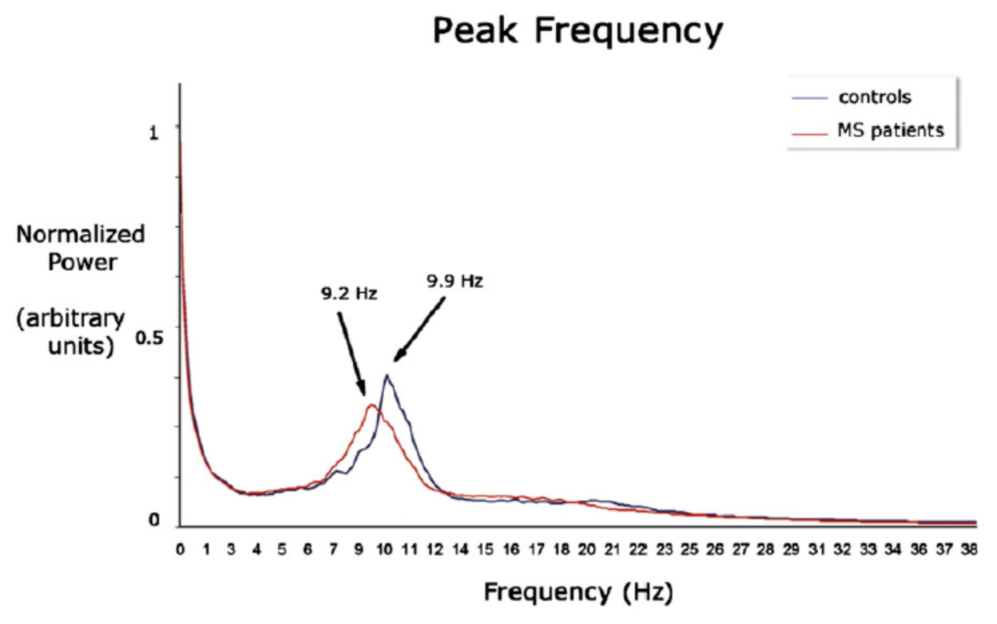
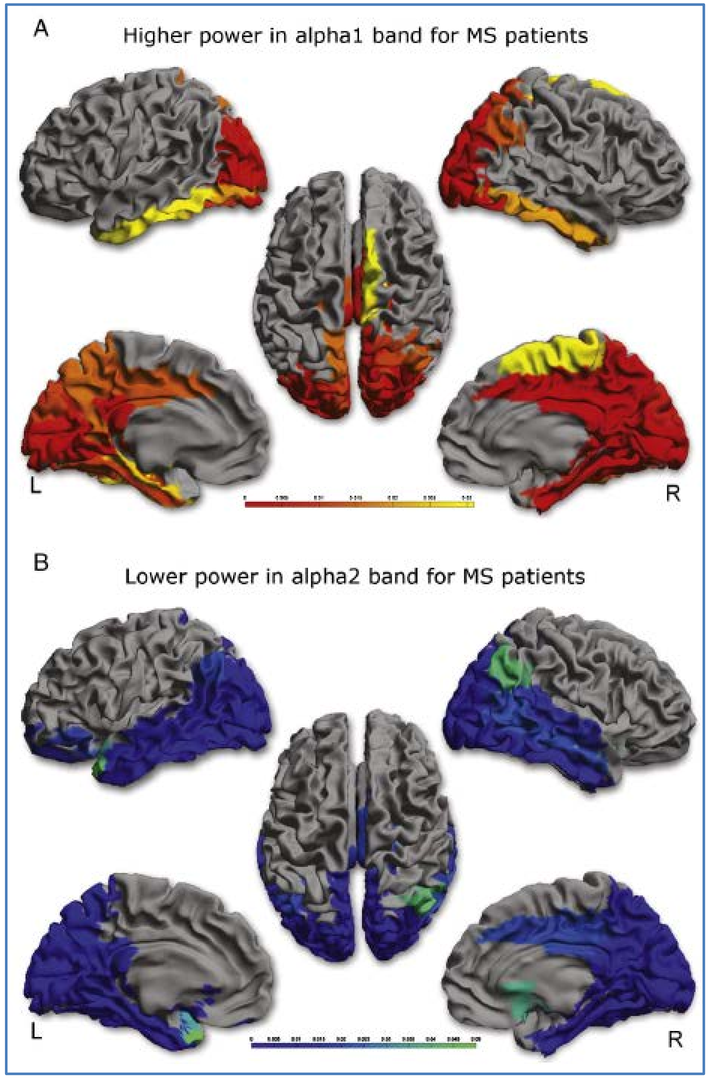


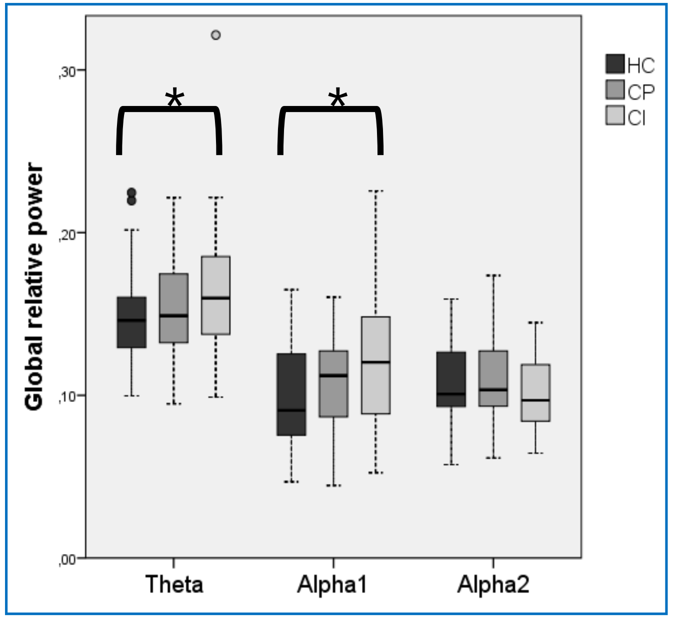
Fig. 2. Normalized power spectra, with peak frequency for patients (9.15 Hz) and for controls (9.92 Hz).


A
Higher power in alpha1 band for MS patients
L
R
B
Lower power in alpha2 band for MS patients
L
R

MS outpatient clinic

- Slowing is even more specifically present in cognitive impaired patients (Schoonhoven *et al.*, submitted)

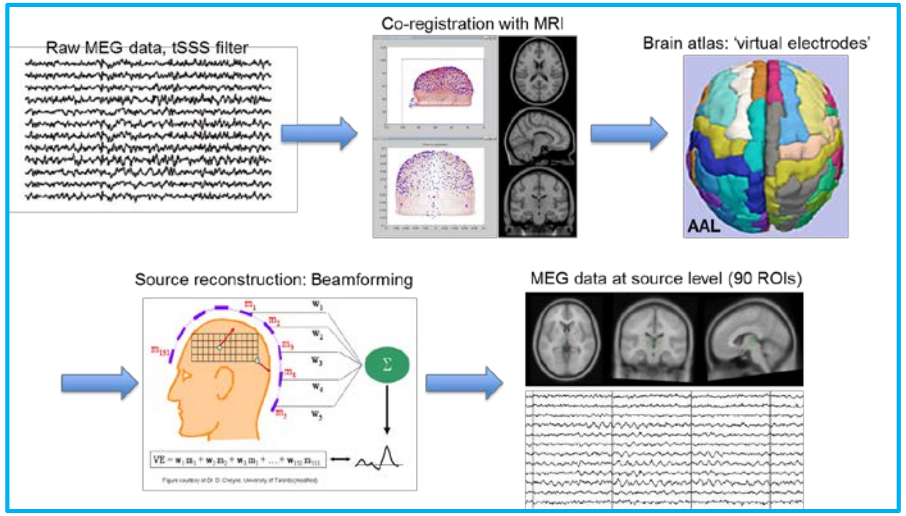
37 cognitively preserved (CP)
28 cognitively impaired (CI)
34 healthy controls (HC)



Cognitive domain	**Frequency band**	**β**	**p-value**
Average cognition	Theta (4-8 Hz)	-0.243	**0.032**
	Alpha 1 (8-10Hz)	-0.304	**0.013**
Verbal memory	Theta (4-8 Hz)	-0.333	**0.024**
	Alpha 1 (8-10Hz)	-0.257	**0.032**
	Gamma (30-48Hz)	0.309	**0.008**
Working memory	Theta (4-8 Hz)	-0.240	**0.032**
	Alpha 1 (8-10Hz)	-0.388	**<0.001**
Attention	Alpha 1 (8-10Hz)	-0.408	**<0.001**
Executive function	-	-	**-**
Information processing speed	-	-	**-**
Verbal fluency	Alpha 1 (8-10Hz)	-0.231	**0.032**
Visuospatial memory	-	-	**-**

Could MEG serve as a biomarker for cognitive impairment in an outpatient clinic?

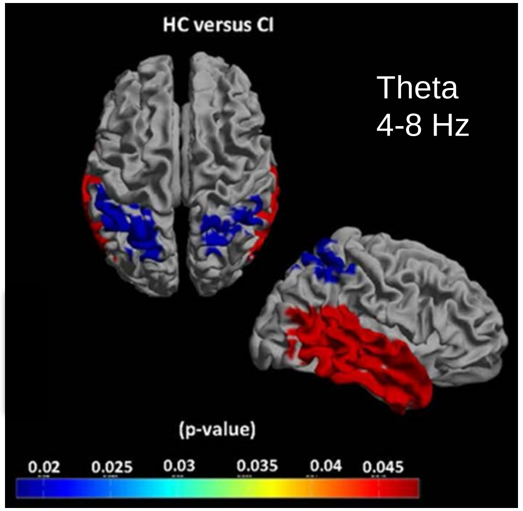
Clinical MEG during MS outpatient clinic


Raw MEG data, tSSS filter
Co-registration with MRI
Brain atlas: 'virtual electrodes'
AAL
Source reconstruction: Beamforming
Σ
MEG data at source level (90 ROIs)

- 1-2 patients MS cognition outpatient clinic per week

- Protocol identical to memory clinic MEG

- MEG report:
  - Visual analysis of abnormalities
  - Frequency analysis (spectra/power)
  - Blinded to clinical context
    - Mild/moderate/severe
    - Diffuse/focal
    - Epileptiform discharges



Case 1: 68 years old male

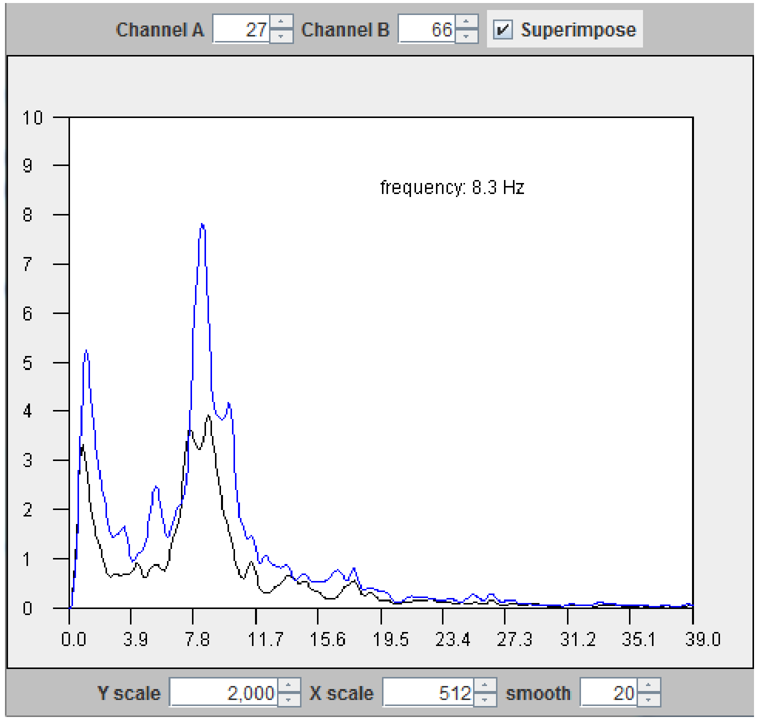
- Second opinion MS and cognition (SOMSCOG) outpatient clinic
- MS since 2005, secondary progressive MS since 2010
- Main complaints:

  forgetfulness, disorientation, walking problems (<100m), fatigue
- Neuropsychological testing

  ↓information processing speed, executive functioning, visuoconstruction

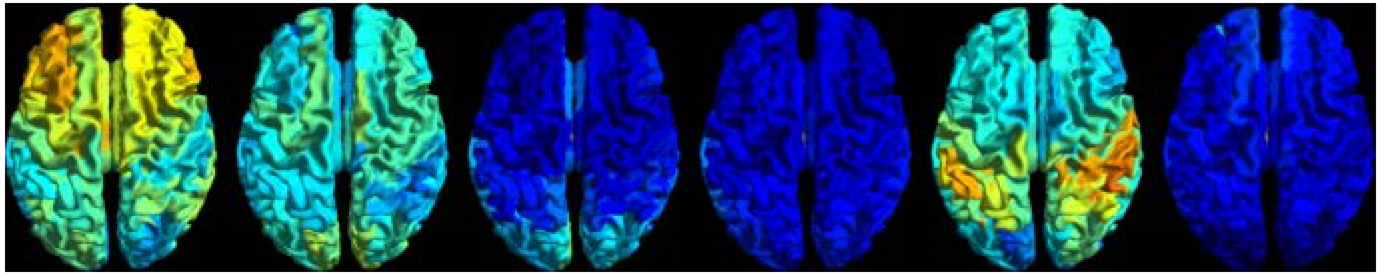
Case 1: Abnormal

Relative power	
Delta (0 – 4Hz)	0.301
Theta (4 – 8 Hz)	0.213
Alfa1 (8 – 10Hz)	0.112
Alfa2 (10 – 13Hz)	0.078
Beta (13 – 30Hz)	0.221
Gamma (30 – 40Hz)	0.077
Average peak frequency	7.384


Channel A 27 Channel B 66 ☑ Superimpose

frequency: 8.3 Hz

Y scale 2,000 X scale 512 smooth 20

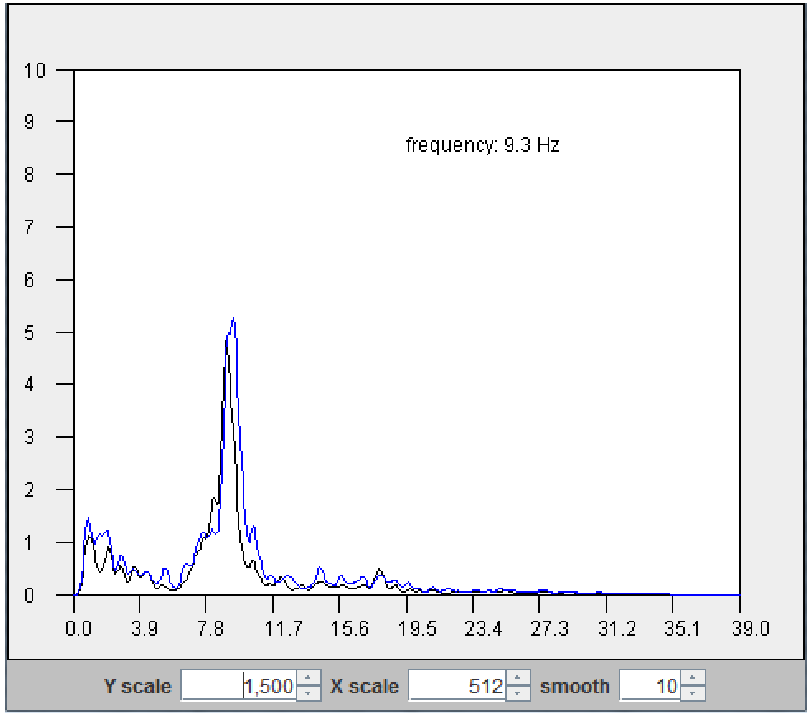

delta **theta** **alfa1** **alfa2** **beta** **gamma**

Case 2: 52 years old female

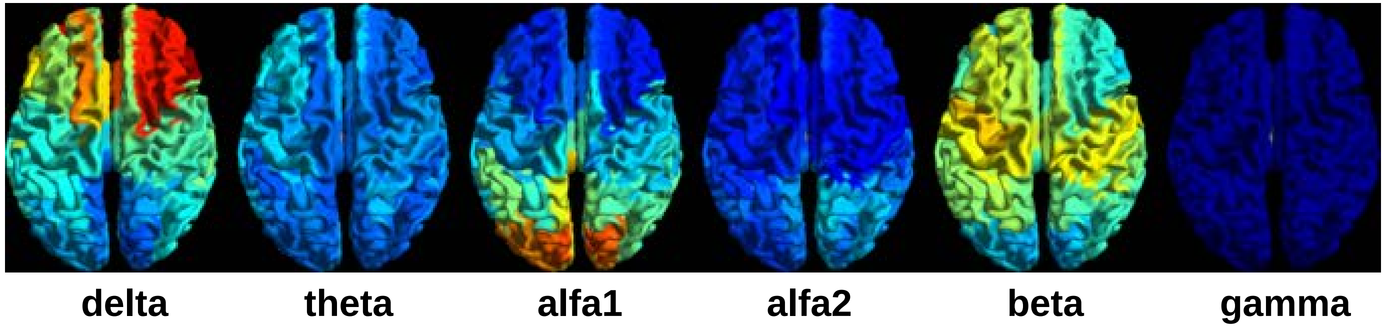
- SOMSCOG clinic
- Relapsing-remitting MS since 2009
- Main complaints: fatigue and painful sensations in legs
- Neuropsychological testing
  - ➢ no abnormalities
  - ➢ no subjective complaints
- Medical student who wonders if it is a good idea to finish her study

Case 2: normal

Relative power values	
Delta (0 – 4Hz)	0.288
Theta (4 – 8 Hz)	0.150
Alfa1 (8 – 10Hz)	0.207
Alfa2 (10 – 13Hz)	0.103
Beta (13 – 30Hz)	0.251
Gamma (30 – 40Hz)	0.001
Average peak frequency	**8.966**



Y scale 1,500 X scale 512 smooth 10



Clinical MS MEG after 1 year

Total number of registrations	70	
Normal registration	47	(67%)
Abnormal registration	22	(31%)
Mild abnormalities	16	(23%) / (73%)
Diffuse slowing	13	
Focal abnormalities	5	
Epileptiform discharges	0	
Severe abnormalities	6	(9%) / (37%)
Diffuse slowing	6	
Focal abnormalities	1	
Epileptiform discharges	1	
No report	1	

Conclusions (Part 2)

- Visual analysis of EEG and MEG provides information for differential diagnosis in dementia, and for diagnosis in SOMSCOG clinic
- Converted clinical EEG protocols to MEG
- Added benefits of MEG include detailed spatial information and patient friendliness
- Novel technologies (OPMs) could reduce cost of MEG and increase its availability

Boto *et al.*, 2018

Acknowledgements

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